particles for imaging, Straub et al. '300 teach porous pharmaceutical particles for drug delivery and such particles can be made to become tablets. The rejections are respectfully traversed.

It is well-established that to constitute anticipation, all material elements of a claim must be found in one prior art source, In re Marshall, 198 USPQ 344 (Fed.Cir. 1978); In re Kalm, 154 USPQ 10 (CCPA 1967), which must be enabling to one skilled in the art. Akzo v. U.S. International Trade Commission, 1 USPQ2d 1241 (Fed.Cir.1986), i.e. enable that person to understand the nature and operation of the invention.

Straub et al. ('698) disclose and claim a method for making a microparticle formed of a synthetic biocompatible polymer *useful as an ultrasound contrast agent.* The microparticle is formed by emulsifying a solution of the synthetic biocompatible polymer. In contrast, the invention herein is directed to *methods for preparing pharmaceutical dosage forms* containing a solid pharmaceutically acceptable volatilizable agent and a pharmaceutically active ingredient.

Hanes et al. ('913) disclose and claim particles incorporating surfactants for drug delivery to the pulmonary system comprising biodegradable particles incorporating a therapeutic, prophylactic or diagnostic agent and surfactant. Unlike Hanes et al. ('913) the instant invention does not utilize biodegradable particles incorporating a therapeutic, prophylactic or diagnostic agent and surfactant.

Straub et al. ('300) teach a method for making a porous matrix of drug comprising an initial step of dissolving a drug in a solvent to form a solution. The purpose of the '300 disclosure is to enhance drug dissolution. In contrast, Applicant's invention does not require an initial step of dissolving a drug in solvent and is not focused on drug dissolution rate. Rather, the intent of the instant invention is to enhance compactibility of the entire drug product.

The disclosure of an assertedly anticipating prior art reference must be adequate to enable possession of desired subject matter, and a reference that names or describes desired subject matter does not anticipate if the subject matter cannot be produced without undue experimentation. Even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling. Elan v. Mayo Foundation, 68 USPQ2d 1373 (Fed.Cir. 2003). Moreover, In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990) states that under 35 USC 102(b), every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim.

Applicant submits the references cited by the Examiner as anticipatory to the invention herein do not meet the statutory requirement. The Examiner cannot seriously consider a reference directed to a method for making a microparticle formed of a synthetic biocompatible polymer *useful as an ultrasound contrast agent* to enable Applicant's dosage forms that are formed by compression and provide enhanced cohesive and compressibility properties. Hanes et al. '913 and Straub et al. '300 are as deficient as Straub et al. '698 in that neither reference discloses every element of Applicant's invention and neither reference enables a skilled artisan to make the present invention without undue experimentation, as is required by 35 USC 102. Clearly, the statutory mandate for a finding of anticipation has not been met. Withdrawal of all rejections under 35 USC 102(b) is requested.

Claims 1-32 and 38 have been rejected under 35 USC 103 as being unpatentable over Straub '300 in view of Remington. The Examiner's comments have been carefully considered, and the rejection is respectfully traversed.

In order to facilitate the Examiner's understanding of the present invention, Applicant offers the following comments with respect to the Figures herein.

Figure 1 demonstrates the effect of wet granulation mixing time on granule formation and granule density. Five Formulation A (no volatilizable agent) wet granulations were manufactured using equivalent process parameters with the variable being mixing time. In all examples, water was used as the wet granulating solvent and was added during the first three

minutes of the wet granulation process. The five wet granulations were manufactured with total mixing times of 3, 5, 10, 15 and 20 minutes. The plots show that mixing time decreases tablet hardness. This decrease in tablet hardness is directly related to granule density. An increased granule density directly decreased granule surface area. The decreased surface area of the granule reduces the area for bonding within the granule structure. The less surface area available for bonding to occur, the lower the tablet strength will be on compression. Thus, over-densification of the granules as a result of wet granulation mixing time will decrease compressibility and lower tablet hardness. The instant application describes a method to increase the surface area, decrease granule density and enhance granule bonding.

A dense granule has limited ability for further densification during compression into a tablet. A hard dense granule will only have the external granule surface available for bonding with other granules to form a tablet. A highly porous granule has a high capacity for further densification. When a porous granule is exposed to the external forces during the tablet compression process, a porous granule will fracture and form additional areas for bonding within the structure of the granule. This results in stronger bond formation between granules and increased tablet hardness.

Figure 2 demonstrates the effect of incorporating 10% ammonium bicarbonate into the formulation as a volatilizable agent. Incorporating a volatilizable agent into the formulation (formulation B) during the wet granulation process and then removing the volatilizable agent by sublimation prior to tablet compression increases the compressibility of the granules. Therefor, formulation B containing the volatilizable agent has an increased tablet hardness over formulation A manufactured without a volatilizable agent. Incorporating the volatilizable agent into the formulation produces a porous granule containing a high surface area and decreased density over granule formation without a volatilizable agent incorporated into the formulation. This increased surface area within the structure of the granule increases the area for bonding to occur between granules and, therefore, increases the strength of the tablet on compression.

Figure 3 demonstrates the effect of the volatilizable agent particle size on granule porosity. The primary particle size of the volatilizable agent is crucial to the degree of granule porosity formed within the structure of the granule. The smaller the primary volatilizable agent particle size incorporated into the formulation, the higher the level of porosity, increased surface area and lower granule density. The smaller the particle size of the volatilizable agent incorporated into the formulation the higher the tablet hardness will be on compression.

The instant application concerns increasing granule porosity as a process related enhancement only to increase tablet strength which is accomplished by increasing area of bonding within the granule structure.

Hanes et al. '913 are preparing, as described in the abstract, "aerodynamically light particles" for pulmonary delivery. The Hanes et al. process for preparing particles is a spray drying process where a solid is dissolved in a solvent (typically an organic solvent) and the solution is sprayed into a heated environment to quickly remove the solvent. Hanes et al. claim particles of 5-30 μm, which is typical for this type process. Hanes et al. state that porosity & surface roughness can be controlled with process parameters. Hanes et al. are not claming the addition of a volatilizable agent in their process to control the particles structure. Hanes et al. state that, "porosity and surface roughness are being controlled by varying the inlet and outlet temperature of the spray drying process". If indeed Hanes et al. are controlling the porosity of their particles, it is the spray drying process controlling the porosity of their product. The porosity in the instant application is being controlled by the addition of a volatilizable agent that is incorporated into the formulation and sublimed to form porous granules of approximately 100-200 μm. As stated earlier in the Figure 3 description, the instant granule porosity is being controlled by the size of the ingoing volatilizable agent.

Straub et al. '300 are also preparing microparticles (0.1–5.0 μm) using a spray drying process and are claiming a porous matrix form of a drug substance to improve dissolution. The disclosed method requires a drug be dissolved in a volatile organic solvent to form a drug

solution. The next step requires the addition of a volatile pore forming agent to form an emulsion, suspension or second solution. The volatile organic solvent and volatile pore forming agent are removed from the emulsion, suspension or second solution to yield a porous matrix having a tap density of less than or equal to 1.0 g/mL or a total surface area of greater than or equal to 0.2 m^2 /g.

According to Straub et al. at column 3, lines 40-60, and at column 4, lines 1-11, the rate of dissolution of drugs is enhanced by making the drug into a porous matrix form. The matrix must contain microparticles of drug, which preferably have a diameter between about 100 nm and 5μm. The drug matrix must be sufficiently porous to yield microparticles having these parameters. The TAP density is preferably less than about 1.0 g/ml, more preferably less than 0.8 g/ml. This level of porosity of the matrix, characterized by density, provides sufficient surface area to enhance wetting of the dry porous matrix and enhance drug dissolution.

In contrast, the instant invention does not require the dissolution steps taught by Straub et al. nor does it require the microparticles of drug having a diameter between about 100 nm and 5μm. Applicant's method utilizes a dry blend of entire drug substance. Unlike Straub et al. who focus on rate of dissolution, Applicant herein has devised a novel method to increase compressibility, which, in turn, increases rate of production and decreases cost. From the disclosure in Straub et al., it is clear that the *porous* matrix enhances the dissolution rate of drugs.

It is respectfully submitted that the porous matrix as disclosed in Straub et al could not be used to make Applicant's invention. This is because Applicant's process, as defined in claim 1, claims a compression step following the step in which a porous second granulate is made (i.e. as the result of volatilizing a solid volatilizable agent from first granules). The compression step follows, with the granules being compressed into a tablet-like dosage form or compressed device. Application of such a compression step would likely destroy the porous matrix taught by Straub et al.